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# Antitumor Activities of Newly Synthesized 5-Carbamoyl-1 *H*-imidazol-4yl 1-Adamantanecarboxylate and 5-Carbamoyl-1 *H*-imidazol-4yl Piperonylate

**Noboru Yoshida, Takao Kiyohara, Masaru Fukui, Toshio Atsumi, Shigeo Ogino, Makoto Inaba,[1] Shigeru Tsukagoshi, and Yoshio Sakurai**

*Research Department, Pharmaceutical Division, Sumitomo Chemical Co., Ltd., 2-1 Takatsukasa 4-chome, Takarazuka 665 [N. Y., T. K., M. F., T. A., S. O.], and Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Kami-Ikebukuro, Toshima-ku, Tokyo 170 [M. I., S. T., Y. S.], Japan*

## ABSTRACT

In synthetic studies on the chemical modification of the nucleoside antibiotic bredinin, two new derivatives, 5-carbamoyl-1*H*-imidazol-4-yl 1-adamantanecarboxylate and 5-carbamoyl-1*H*-imidazol-4-yl piperonylate, were found to possess a potent antitumor activity in several experimental tumor systems, even though bredinin itself shows only *in vitro* cytotoxicity and thus lacks therapeutic effectiveness.

These two derivatives of bredinin exhibited antitumor activity against a wide variety of tumors, including leukemias L1210 and P388, Lewis lung carcinoma, B16 melanoma, Colon 26 and 38 adenocarcinomas, Ehrlich carcinoma, and Sarcoma 180. It is noteworthy that these agents showed good therapeutic effects not only against ascitic types of tumors but also against a number of slow-growing solid tumor lines, particularly the ascitic and solid forms of Ehrlich carcinoma. At their optimal doses, both compounds effected a complete cure of all or most of the mice treated.

Although the mechanisms of action of these compounds remain unknown, they are able to suppress *in vivo* tumor growth, presumably by being slowly anabolized *in vivo* to an active form and inhibiting purine *de novo* synthesis as bredinin does.

## INTRODUCTION

A nucleoside derivative of 4-amino-5-imidazolecarboxamide riboside, bredinin (4-carbamoyl-1-$\beta$-D-ribofuranosylimidazolium 5-olate), has been reported to possess *in vitro* cytotoxic activity against mammalian cells such as L5178Y leukemia (4, 6) but exhibits at most very weak *in vivo* antitumor activity against L1210 leukemia and Ehrlich carcinoma (3). Its aglycone, 4-carbamoylimidazolium 5-olate, shows a significant *in vitro* cytotoxicity but only weak *in vivo* activity against some experimental tumors.

We thought it possible that the aglycone could be endowed with *in vivo* antitumor activity by an appropriate alteration in its chemical structure and, thus, in its pharmacological properties. Among a number of synthesized derivatives, the following 2 new compounds, SL-1233[2] and SL-1250, were found to possess marked antitumor activities. In this paper, we describe the antitumor effects of SL-1233 and SL-1250 against various murine tumors.

## MATERIALS AND METHODS

**Drugs.** SL-1233 and SL-1250, new derivatives of imidazolecarboxamide, were synthesized in our laboratory.[3] Briefly, SL-1233 and SL-1250 were prepared by acylation of anhydro-4-carbamoyl-5-hydroxyimidazolium hydroxide with 1-adamantanecarbonyl chloride or 3,4-methylenedioxybenzoyl chloride in pyridine. Both compounds were recrystallized from dimethyl sulfoxide/water to give white crystalline compounds with melting points of 208° (with decomposition) and 215° (with decomposition), respectively. These compounds were virtually insoluble in aqueous media and were suspended in 0.85% NaCl solution containing 0.5 to 2.0% (w/v) Tween 80 or 5% (w/v) gum arabic. The aqueous suspensions of SL-1233 and SL-1250 were prepared immediately before use or stocked in a freezer and were administered either i.p. or p.o. to tumor-bearing mice at the volume of 0.1 ml/10 g body weight.

**Animals and Tumors.** Five- to 8-week-old male C57BL/6 × DBA/2 $F_1$ (hereafter called B6D2$F_1$) mice were used in the chemotherapy experiments on Lewis lung carcinoma, mouse melanoma B16, and Colon 38 carcinoma. Female BALB/c × DBA/2 $F_1$ (hereafter called CD2$F_1$) mice of the same age were used for the chemotherapy experiments on Colon 26 carcinoma and P388 and L1210 leukemias. Male ICR mice, 5 to 6 weeks old, were used for the chemotherapy experiments on Sarcoma 180 and Ehrlich carcinoma.

Groups of 6 to 8 mice were housed in plastic cages and were given water and pelleted food *ad libitum*. L1210 and P388 leukemias were maintained by continuous i.p. passage in syngeneic male DBA/2 mice. B16 melanoma and Lewis lung carcinoma were carried s.c. in syngeneic female C57BL/6 mice. Colon 26 and 38 adenocarcinomas were carried in syngeneic female BALB/c and C57BL/6 mice, respectively. Sarcoma 180 and Ehrlich carcinoma were maintained by continuous passage in male ICR mice. All mice of these strains were purchased from Charles River Japan, Inc. (Kanagawa, Japan).

Standardized protocols of the Drug Research and Development Program, National Cancer Institute (1), were followed for continuous passage of the tumors and for implantation of tumors into B6D2$F_1$ or CD2$F_1$ mice for the chemotherapy

[1] To whom requests for reprints should be addressed.

[2] The abbreviations used are: SL-1233, 5-carbamoyl-1*H*-imidazol-4-yl 1-adamantanecarboxylate; SL-1250, 5-carbamoyl-1*H*-imidazol-4-yl piperonylate; DTIC, 5-(3,3'-dimethyl-1-triazeno)imidazole-4-carboxamide.

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[3] Y. Tarumi, Y. Takebayashi, K. Moriguchi, T. Atsumi, T. Fukumaru, and H. Yamamoto. Reactions of novel antineoplastic acyl derivatives of 4-carbamoylimidazolium-5-olate, submitted for publication.

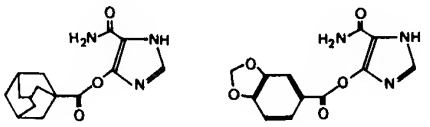
experiments.

L1210 and P388 leukemias were implanted i.p. at $10^5$ and $10^6$ viable cells/mouse, respectively. B16 melanomas were implanted i.p. or s.c. as 0.5 ml of a 1/10 (w/v) tumor brei. Lewis lung carcinomas were implanted s.c. ($10^6$ viable cells). Colon 38 was implanted s.c. using trocar fragments of nonnecrotic tissue. Colon 26 was implanted i.p. as 0.5 ml of a 1/100 (w/v) tumor brei. Sarcoma 180 and Ehrlich carcinoma were implanted i.p. or i.m. ($10^6$ ascitic cells/mouse).

The growth of s.c.-implanted Lewis lung carcinoma and B16 melanoma or of i.m.-implanted Ehrlich carcinoma was monitored by measurement of perpendicular diameters with vernier calipers. Tumor weight in mg was estimated by the formula for the volume of a prolate ellipsoid, assuming unit density: ½ x major diameter (mm) x minor diameter (sq mm). The tumor measurements were made twice a week.

## RESULTS

Activities of the synthesized compounds derived from 4-carbamoylimidazolium 5-olate, the basic structure of bredinin (3), underwent preliminary evaluation in the solid form of Sarcoma 180. Among a number of derivatives tested, the following 2 new compounds, SL-1233 and SL-1250 (Chart 1), were found to possess relatively higher suppressive effectiveness against the growth of tumor masses. Further studies revealed that SL-1233 and SL-1250 showed great effectiveness against several experimental tumors, including Ehrlich carcinoma, Lewis lung carcinoma, Colon 26 and 38 carcinomas, and mouse L1210 and P388 leukemias. In addition, they possessed a definitive, but not potent, activity against B16 melanoma implanted i.p.



SL-1233 SL-1250

Chart 1. Chemical structures of SL-1233 and SL-1250.

Ehrlich carcinomas, in either the ascitic or solid form, were the tumors most susceptible to both SL-1233 and SL-1250. The data in Table 1 indicate that both compounds when administered over a very broad dose range by daily i.p. injection, possess extremely potent antitumor activity against i.p.-implanted Ehrlich carcinomas. All mice tested survived more than 90 days at the optimal dose of these compounds. When compared under the experimental conditions shown in Table 1, SL-1233 and SL-1250 were much more effective against this tumor than were 3 other antitumor agents available clinically (5-fluorouracil, methotrexate, and 1-β-D-arabinofuranosylcytosine) with respect to potency of antitumor activity and effective dose range.

These compounds were virtually insoluble in water. Therefore, the therapeutic efficacy of their p.o. administration will be a subject of discussion. In this respect, the data shown from Experiments 2 and 3 in Table 1 clearly demonstrate that SL-1233 and SL-1250 administered p.o. possess potent activity against Ehrlich carcinoma, although a higher dose is needed than for i.p. injection. Nonetheless, significant prolongation of life resulted even with treatment at the lower dose of 50 mg/kg.

Table 2 shows the therapeutic efficacy of SL-1233 and SL-1250 against the solid form of Ehrlich carcinoma. Daily administrations (Days 1 to 9) of these 2 drugs either i.p. or p.o.

Table 1

*Effects of SL-1233 and SL-1250 on survival of mice bearing i.p. Ehrlich carcinoma*

| Experiment | Drug | Route | Dose (mg/kg)[a] | Survival time (days) | | % of increased life span | Survivors (Day 90) |
|---|---|---|---|---|---|---|---|
| | | | | Median | Range | | |
| 1 | Control | | | 26.0 | 19-45 | | 0/8 |
| | SL-1233 | i.p. | 6.2 | 42.0 | 27->90 | 61 | 2/8 |
| | | | 12.5 | >90 | 56->90 | >246 | 5/8 |
| | | | 25 | >90 | >90 | >246 | 8/8 |
| | | | 50 | >90 | 60->90 | >246 | 7/8 |
| | | | 100 | >90 | 3->90 | >246 | 7/8 |
| | SL-1250 | i.p. | 3.1 | 56.0 | 33->90 | 115 | 2/8 |
| | | | 6.2 | >90 | 48->90 | >246 | 4/8 |
| | | | 12.5 | >90 | 52->90 | >246 | 6/8 |
| | | | 25 | >90 | >90 | >246 | 8/8 |
| | | | 50 | >90 | 10->90 | >246 | 6/8 |
| 2 | Control | | | 20.0 | 17-26 | | 0/8 |
| | SL-1233 | p.o. | 25 | 24.2 | 21-26 | 21 | 0/8 |
| | | | 50 | 31.7 | 24->90 | 58 | 2/8 |
| | | | 100 | >90 | 31->90 | >350 | 5/8 |
| | | | 200 | >90 | 53->90 | >350 | 7/8 |
| | | | 400 | >90 | 9->90 | >350 | 4/8 |
| 3 | Control | | | 21.7 | 18-40 | | 0/8 |
| | SL-1250 | p.o. | 25 | 25.0 | 23-30 | 15 | 0/8 |
| | | | 50 | 35.0 | 26->90 | 60 | 3/8 |
| | | | 100 | >90 | 8->90 | >300 | 4/8 |
| | | | 200 | >90 | 12->90 | >300 | 6/8 |
| | | | 400 | >90 | 8->90 | >300 | 5/8 |

[a] Daily administration on Days 1 to 9.

Table 2
*Effects of SL-1233 and SL-1250 on solid Ehrlich carcinoma*

| Drug | Schedule | Route | Dose (mg/kg) | Tumor inhibition (%)[a] Day 21 | Tumor inhibition (%)[a] Day 45 | Survivors/8 mice Day 60 | Survivors/8 mice Day 90 | Tumor free/8 mice (Day 90) |
|---|---|---|---|---|---|---|---|---|
| Control | | | | | | 2 | 1 | 0 |
| SL-1233 | 9QD[b] | i.p. | 6.2 | 62.5 | 36.9 | 6 | 1 | 0 |
| | | | 12.5 | 61.7 | 19.5 | 8 | 0 | 0 |
| | | | 25 | 91.8 | 48.9 | 8 | 3 | 1 |
| | | | 50 | 96.8 | 71.1 | 8 | 5 | 4 |
| | | | 100 | 96.7 | 87.2 | 6 | 6 | 3 |
| | 9QD | p.o. | 12.5 | 64.5 | 24.8 | 5 | 1 | 0 |
| | | | 25 | 75.5 | 34.9 | 8 | 2 | 1 |
| | | | 50 | 91.1 | 74.1 | 8 | 4 | 3 |
| | | | 100 | 95.0 | 78.2 | 8 | 6 | 2 |
| | | | 200 | 95.8 | 82.3 | 7 | 5 | 5 |
| | | | 400 | 96.9 | 91.2 | 3 | 3 | 2 |
| Control | | | | | | 4 | 0 | 0 |
| SL-1250 | 9QD | i.p. | 3.1 | 36.2 | 0 | 4 | 0 | 0 |
| | | | 6.2 | 35.6 | 0 | 7 | 0 | 0 |
| | | | 12.5 | 82.1 | 54.1 | 8 | 2 | 1 |
| | | | 25 | 97.4 | 91.3 | 7 | 6 | 4 |
| | | | 50 | 96.8 | 98.7 | 3 | 2 | 2 |
| | 3Q4D | i.p. | 18.8 | 34.4 | 5.8 | 4 | 1 | 0 |
| | | | 37.5 | 62.5 | 54.0 | 7 | 3 | 1 |
| | | | 75 | 95.0 | 96.4 | 8 | 7 | 5 |
| | | | 150 | 95.8 | 98.6 | 8 | 8 | 8 |
| | 9QD | p.o. | 12.5 | 18.2 | 1.2 | 7 | 0 | 0 |
| | | | 25 | 79.0 | 54.1 | 8 | 1 | 1 |
| | | | 50 | 87.7 | 57.9 | 8 | 2 | 1 |
| | | | 100 | 94.3 | 87.3 | 8 | 5 | 1 |
| | | | 200 | 95.6 | 93.8 | 8 | 6 | 3 |
| | | | 400 | 94.6 | 98.1 | 3 | 3 | 2 |

[a] Tumor mass growth inhibition: $(1 - T/C) \times 100\%$.
[b] 9QD, daily administration, Days 1 to 9; 3Q4D, 3 doses, one each on Days 1, 5, and 9.

inhibited the growth of the tumor mass to great extent on Day 21 and even on Day 45. It is also worth noting that SL-1250 inhibited tumor growth completely when administered by intermittent i.p. injections (150 mg/kg/day on Days 1, 5, and 9).

SL-1233 and SL-1250 were also effective against syngeneic tumors such as Lewis lung carcinoma and Colon 26 and Colon 38 carcinomas. These drugs caused significant delays in tumor growth in Lewis lung carcinomas (Chart 2). This delay in tumor growth was assumed to be responsible for the prolongation of the life of the treated mice. The established tumor mass of Lewis lung carcinoma was not reduced by the delayed therapy starting 8 days after tumor implantation; however, the treated mice survived as long as did those that received the early treatment (Table 3).

Colon 26 carcinoma responded well to SL-1233 and SL-1250 (Table 4). SL-1250 showed greater than 100% increased life span at dose levels from 6.3 to 100 mg/kg/day (Days 1 and 5) when administered i.p.

The data shown in Table 5 represent schedule dependence as well as therapeutic efficacy of these compounds against mouse leukemia P388. Intermittent and daily treatments had significantly better therapeutic effectiveness than did a single injection, particularly with SL-1233, when the respective optimal doses of these 3 treatment schedules were compared. These results also indicate that these compounds possess

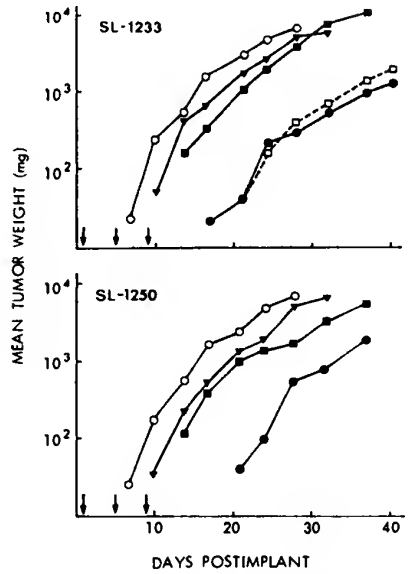



Chart 2. Effects of SL-1233 and SL-1250 on the growth of s.c.-implanted Lewis lung carcinoma. The drug was administered i.p. on Days 1, 5, and 9 (*arrows*). ○, untreated control; □, 200 mg/kg/day; ●, 100 mg/kg/day; ■, 50 mg/kg/day; ▼, 25 mg/kg/day.

Table 3

*Effects of SL-1233 and SL-1250 on survival of mice bearing s.c. Lewis lung carcinoma by early or delayed treatments*

| Drug | Dose (mg/kg) | Treatment on Days 1, 5, and 9 | | | | Treatment on Days 8, 12, and 16 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Median | Range | % of increased life span | Survivors (Day 60) | Median | Range | % of increased life span | Survivors (Day 60) |
| SL-1233 | 200 | >60 | 42->60 | >128 | 3/6 | 29.0 | 21-49 | 10 | 0/6 |
| | 100 | >60 | 43->60 | >128 | 3/6 | 45.0 | 33->60 | 71 | 1/6 |
| | 50 | 39.0 | 32-42 | 48 | 0/6 | 37.0 | 24-43 | 40 | 0/6 |
| | 25 | 37.0 | 32-40 | 40 | 0/6 | 37.0 | 25->60 | 40 | 1/6 |
| SL-1250 | 200 | 42.0 | 7->60 | 59 | 2/6 | 35.0 | 16-54 | 33 | 0/6 |
| | 100 | 45.0 | 38->60 | 72 | 1/6 | 33.0 | 23-49 | 25 | 0/6 |
| | 50 | 41.8 | 35->60 | 58 | 1/6 | 42.3 | 38->60 | 60 | 1/6 |
| | 25 | 37.3 | 28-45 | 41 | 0/6 | 37.3 | 17-42 | 41 | 0/6 |
| Untreated control | | 26.3 | 17-35 | | 0/6 | | | | |

Table 4

*Effects of SL-1233 and SL-1250 on survival of mice bearing i.p. Colon 26 carcinoma*

| Drug | Dose[a] (mg/kg) | Survival time (days) | | % of increased life span | Survivors (Day 60) |
|---|---|---|---|---|---|
| | | Median | Range | | |
| SL-1233 | 200 | 37.0 | 25->60 | 68 | 2/7 |
| | 100 | >60 | 22->60 | >172 | 5/7 |
| | 50 | 28.0 | 22->60 | 27 | 3/7 |
| | 25 | 31.0 | 22-56 | 40 | 0/7 |
| | 12.5 | 28.0 | 23-53 | 29 | 0/7 |
| | 6.2 | 29.0 | 23-37 | 31 | 0/7 |
| SL-1250 | 200 | 9.1 | 7-10 | Toxic | 0/7 |
| | 100 | >60 | 8->60 | >172 | 6/7 |
| | 50 | 49.0 | 36->60 | 122 | 3/7 |
| | 25 | 47.0 | 39->60 | 113 | 2/7 |
| | 12.5 | >60 | 26->60 | >172 | 5/7 |
| | 6.2 | 44.0 | 26->60 | 100 | 3/7 |
| | 3.1 | 24.2 | 20-26 | 10 | 0/7 |
| Untreated control | | 22.0 | 18-24 | | 0/7 |

[a] Administration i.p. on Days 1 and 5.

Table 5

*Effect of SL-1233 and SL-1250 on survival of mice bearing P388 leukemia: schedule dependence*

| Treatment schedule (days) | SL-1233 | | SL-1250 | |
|---|---|---|---|---|
| | Dose[a] (mg/kg) | % of increased life span | Dose (mg/kg) | % of increased life span |
| 1 | 266 | 15 | 93 | 32 |
| | 346 | 32 | 121 | 53 |
| | 450 | 15 (2)[b] | 158 | 53 |
| | | | 205 | 53 |
| | | | 266 | 60 (3) |
| 1, 5, 9 | 121 | 43 | 55 | 42 |
| | 158 | 53 | 72 | 48 |
| | 205 | 42 | 93 | 64 |
| | 266 | 51 | 121 | 90 |
| | 346 | 53 (2) | 158 | 86 |
| | | | 205 | −17 (4) |
| 1-9 | 25 | 37 | 19 | 48 |
| | 33 | 56 | 25 | 60 |
| | 42 | 61 | 33 | 67 |
| | 55 | 61 | 42 | 74 |
| | 72 | 57 | 55 | 80 |
| | 93 | 42 | 72 | 20 (1) |

[a] Injection i.p.

[b] Numbers in parentheses, mice which died of toxicity before the untreated mice did. Each group consists of 6 mice.

potent antiproliferative activity against leukemia at a relatively wide dose range.

The antitumor activities of SL-1233 and SL-1250 against the other tumors are summarized in Table 6. Although significant antitumor effects were observed against Sarcoma 180, these were apparently inferior to those against Ehrlich carcinoma. Both compounds exhibited a limited antitumor effect against L1210 leukemias and B16 melanomas, implanted i.p., while Colon 38 carcinoma, a solid-type tumor, responded well to these 2 drugs.

## DISCUSSION

SL-1233 and SL-1250 showed marked antitumor activities against not only ascitic but against solid tumors such as Lewis lung carcinoma, Colon 26 and 38 adenocarcinomas, and Ehrlich carcinoma. Among the various tumor lines examined, Ehrlich carcinoma, particularly ascitic Ehrlich carcinoma, responded best to these compounds. At optimal doses, these 2 drugs suppressed tumor growth completely, curing the tumor-bearing mice. Both i.p. and p.o. administrations of these compounds were markedly effective against solid as well as against ascitic forms of Ehrlich carcinoma.

In treating cancer, emphasis is placed on therapy for the so-called "slowly growing" solid tumors. SL-1233 and SL-1250 were markedly active against solid tumors such as Ehrlich carcinoma, Lewis lung carcinoma, B16 melanoma implanted i.p., and Colon 26 and Colon 38 carcinomas. The activity of SL-1250 against the solid form of Ehrlich carcinoma was particularly remarkable. The drug completely inhibited the growth of the tumor mass for more than 90 days, and no recurrence of the tumor was observed thereafter.

As compared with the untreated controls, the primary tumor mass of s.c.-implanted Lewis lung carcinomas was suppressed, and the proliferation of the tumor mass was significantly delayed. This delay of tumor growth caused by SL-1233 and SL-1250 is believed to contribute to the prolongation of life for the treated mice. Although the primary tumor evidently was not suppressed by treatment of the tumor at an advanced stage, similar prolongation of life was observed. This may be due to the inhibitory effect of the drugs on the fatal metastatic focus in the lung or elsewhere.

Table 6
*Activities of SL-1233 and SL-1250 against other experimental tumor lines*

| | | | Prolongation of life span | | | | Inhibition of tumor mass growth | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | SL-1233 | | SL-1250 | | SL-1233 | | SL-1250 | |
| Tumor | System | Schedule (days) | Optimal dose (mg/kg) | Maximal % ILS[a] | Optimal dose (mg/kg) | Maximal % ILS | Optimal dose (mg/kg) | Maximal IR %[b] | Optimal dose (mg/kg) | Maximal IR % |
| Sarcoma 180 | i.m.-i.p. | 1-9 | 100 | 18 | 12.5 | 7 | 100 | 55 | 50 | 76 |
| | i.p.-i.p. | 1-9 | 100 | 91 | 12.5-25 | 113 | | | | |
| B16 | s.c.-i.p. | 1-9 | 25 | 35 | 12.5 | 20 | 100 | 56 | 25 | 42 |
| | i.p.-i.p. | 1-9 | 100 | 61 | 25 | 43 | | | | |
| Colon 38 | s.c.-i.p. | 2, 9 | | | | | 200 | 89 | 100 | 78 |
| L1210 | i.p.-i.p. | 1, 5, 9 | 100-400 | 46 | 100 | 69 | | | | |

[a] % ILS, percentage of increased life span.
[b] IR %, inhibition ratio of tumor mass growth on Day 21: $(1 - T/C) \times 100\%$.

Both SL-1233 and SL-1250 exhibited significant activity against L1210 and P388 mouse leukemias and ascitic Sarcoma 180. Results of the schedule dependence of these compounds using P388 leukemia suggested better effectiveness by daily and intermittent treatments, particularly with SL-1233, as compared to a single injection. Among the tumor lines examined, only s.c.-implanted B16 melanoma and s.c.-implanted Sarcoma 180 responded poorly to these compounds, at least with respect to subsequent prolongation of life.

As a whole, these results clearly demonstrate high antitumor activity against a broad spectrum of murine tumors by both SL-1233 and SL-1250. It is also noteworthy that these compounds are effective at a relatively broad dose range, indicating a good therapeutic index.

Although the chemical structures of SL-1233 and SL-1250 are similar to that of DTIC with regard to imidazolecarboxamide derivatives, the mechanism of action of each seems to be different. It has been reported that the antitumor activity of DTIC depends on its triazeno groups rather than on its imidazolecarboxamide in the molecule and that DTIC should be included in the category of alkylating agents (2, 7). On the other hand, Sakaguchi *et al.* have suggested that bredinin is an inhibitor of purine *de novo* synthesis because its ability to inhibit the growth of cultured L5178Y cells is prevented by GMP (4). Furthermore, the aglycone of bredinin was observed to be converted to bredinin in rats (5). On the basis of these observations, we would speculate that SL-1233 and SL-1250, as well as their aglycone, exert their cytotoxic effect after being transformed to bredinin.

Both bredinin and its aglycone showed *in vitro* growth-inhibitory activity against L5178Y cells at almost the same concentration (5). SL-1233 and its aglycone also suppressed *in vitro* growth of Ehrlich carcinoma at similar concentrations (data not shown). In terms of their therapeutic activity, however, SL-1233 and SL-1250 present a striking contrast to bredinin and its aglycone. This difference in their antitumor activity *in vivo* may be due to a long retention time or to a slower clearance of SL-1233 and SL-1250 in the host body.

It is also probable that SL-1233 and SL-1250 are transport forms of bredinin or its aglycone because of lipophilic substitutional groups such as adamantoyl and piperonyloyl moieties which protect these compounds from *in vivo* degradation. The biochemical and pharmacological actions of these compounds are presently under investigation.

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